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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
CELSA, BENNETT M	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 05/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/802,080	DASSEUX ET AL.	
	Examiner	Art Unit	
	Bennett Celsa	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-127* is/are pending in the application.

4a) Of the above claim(s) *64,65,102,105-109 and 111-127* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63,66-101,103,104 and 110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 63-127 are currently pending.

Claims 64-65, 102, 105-109 and 111-127 are withdrawn from consideration as being directed to a nonelected invention.

Claims 63, 66-101, 103-104 and 110 are under consideration to the extent of the elected invention. .

Election/Restrictions

1. Applicant's election of Group I (claims 63-118) in the reply filed on 2/4/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 119-127 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

3. Applicant's further election of seq. Id. 4 (PVLDLFRELLNELLEALKQKLK: 22 AMINO ACIDS), which is asserted to read on claims 68-101, 103(in part) and 104-110 in the reply filed on 2/4/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims Readable on the elected invention (e.g. Group I and seq. id. 4)

a. It would appear applicant inadvertently failed to include claims 63, 66 and 67

to which claim 68 directly/indirectly depends. Accordingly, these claims are being included within the elected invention.

b. It would appear that applicant inadvertently included deletion and conservative analog generics which do not read on the elected species. In this respect, the elected 22 amino acid peptide is within the scope of the elected generic of item (i) of claim 94 but not the deletion generic (ii) or the "altered form" conservative generic (iii) of claim 94. IN this regard, it is again noted that the previous restriction/election requirement restricted out the deletion analogs as a separate invention. Accordingly: claims 111-118 (deletion analogs) and claims 105-109, ("altered form" conservative analogs) are withdrawn from consideration. Thus, claim 94 is being considered in part i.e. the formula (i) generic has been elected.

4. Claims 64-65, 102, 105-109 and 111-118 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention.

Claim Rejections - 35 USC § 112

1. Claims 63 and 66-93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (NEW MATTER REJECTION).

New claims 63 and 66-93 were filed in a Preliminary Amendment dated 3/15/04 filed concurrently with the present application. It is noted that the Preliminary

Amendment though filed with the Declaration, nevertheless is not original subject matter since the Declaration fails to make reference to the filed Preliminary Amendment. For these newly added claims applicant states that support can be found throughout the specification and in the originally presented claims. The originally presented claims are drawn to pharmeceutical compositions comprising:

(i) a 22-29 residue peptide of formula (I) (elected invention);

(ii) a 15-26 reisidue peptide ... consecutive residues selected from residues selected from residues X1 to X23 of formula (I);

(iii) a 22-29 residue altered peptide ... substituted with another residue ...

See original claim 1 (and claims dependent thereon) and present claim 94 (and claims dependent thereon).

However, upon review of the specification and the original claims the Examiner was unable to locate direct or exemplary support for pharmaceutical compositions of the presently claimed scope which possess the specific terminology presented in the present claims 63 and 66-93. In fact, the specification seems to teach that only specific core structure produces the requisite pharmaceutical activity and other attributes (e.g. favorable LCAT activation/helicity/ % hydrophobicity; charged residues/mean hydrophobic moment/mean hydrophobicity/pho angle) recited in claims 63 and 66-93. One of ordinary skill in the art would not deem applicant in possession of other undiscovered core structure (peptide or non-peptide) having these attributes when applicant:

a. provides only one core structure;

b. indicates that this core structure is critical to pharmaceutical activity (e.g. see specification pages 25-27).

Accordingly, applicant must cancel the new matter; or alternatively provide direct support for claiming pharmaceutical compositions of the claim 63 scope possessing the individual attributes defined in the dependent claims.

2. Claims 63 and 66-93 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (WRITTEN DESCRIPTION REJECTION).

It is first noted that written description is legally distinct from enablement: "Although the two concepts of are entwined, they are distinct and each is evaluated under separate legal criteria. The written description requirement, a question of fact, ensures the that the inventor conveys to others that he or she had possession of the claimed invention; whereas, the enablement requirement, a question of law, ensures that the inventor conveys to others how to make and use the claimed invention." See 1242 OG 169 (January 30, 2001) citing *University of California v. Eli Lilly & Co.*

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter

sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

The presently claimed invention broadly encompasses Apo-A-1 agonist compounds which possess attributes (e.g. favorable LCAT activation/helicity/ % hydrophobicity; charged residues/mean hydrophobic moment/mean hydrophobicity/pho angle) but no chemical structure is recited. The term "Apo-A-1 agonist" is an unduly broad term which may refer to analogous structure (e.g. amino acid sequence) and/or function (e.g. therapeutic properties) and/or conformation (e.g. the 3D parameters for binding an enzyme, antibody and/or receptor); the parameters of which is neither described, nor representative examples provided. Additionally, Agonists may encompass non-peptide compounds which are not disclosed nor taught in the specification.

In support thereof, applicant exemplifies

pharmaceutical compositions comprising:

(i) a 22-29 residue peptide of formula (I) (elected invention);

(ii) a 15-26 reisidue peptide ... consecutive residues selected from residues selected from residues X1 to X23 of formula (I);

(iii) a 22-29 residue altered peptide ... substituted with another residue ...

See original claim 1 (and claims dependent thereon) and present claim 94 (and claims dependent thereon).

Neither, the specification, or the original claims provide direct or exemplary support for pharmaceutical compositions of the presently claimed compound scope which possess the specific terminology presented in the present claims 63 and 66-93. In fact, the specification seems to teach that only specific core structure produces the requisite pharmaceutical activity and other attributes (e.g. favorable LCAT activation/helicity/ % hydrophobicity; charged residues/mean hydrophobic moment/mean hydrophobicity/pho angle) recited in claims 63 and 66-93. One of ordinary skill in the art would not deem applicant in possession of other undiscovered core structure (peptide or non-peptide) having these attributes when applicant:

a. provides only one core structure;

b. indicates that this core structure is critical to pharmaceutical activity (e.g. see specification pages 25-27).

Accordingly, applicant has failed to demonstrate possession of all agonist compounds which possess the recited properties as presently claimed. In this regard, applicant is further referred to *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997); "Guidelines for Examination of Patent Applications Under the 35 USC 112, first paragraph, 'Written Description' Requirement" published in 1242 OG 168-178 (January 30, 2001); and Univ. Of Rochester v G. D. Searle and Co. 249 F. Supp. 2d 216 (W.D.N.Y. 2003) affirmed by the CAFC on February 13, 2004 (03-1304) 69 USPQ2d 1886.

3. Claims 63 and 66-93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for pharmaceutical compositions comprising peptide analogues of claim 94 and resulting lipid complexes which are full- length peptides of formula I wherein each bond between residues X1-X23 and the bonds between residues of the peptide of Z2 is an amide linkage the specification does not adequately describe and/or enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims.

2. The nature of the invention

3. The state of the prior art;

4. The level of one of ordinary skill

5. The level of predictability in the art;

6. The amount of direction provided by the inventor;

7. The presence or absence of working examples;

8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure;

See :*In re Wands* USPQ 2d 1400 (CAFC 1988):

(1-2) The breadth of the claims and the nature of the invention:

The presently claimed invention broadly encompasses Apo-A-1 agonist compounds which possess attributes (e.g. favorable LCAT activation/helicity/ % hydrophobicity; charged residues/mean hydrophobic moment/mean hydrophobicity/pho angle) but no chemical structure is recited. The term "Apo-A-1 agonist" is an unduly broad term which may refer to analogous structure (e.g. amino acid sequence) and/or function (e.g. therapeutic properties) and/or conformation (e.g. the 3D parameters for binding an enzyme, antibody and/or receptor); the parameters of which is neither described, nor representative examples provided. Additionally, Agonists may encompass non-peptide compounds which are not disclosed nor taught in the specification.

(3 and 5) *The state of the prior art and the level of predictability in the art:*

The specification clearly describes (e.g. see pages 25-46) that the peptides must conform to various structural requirements in order to display the expected utility (e.g. Apo-A1 agonists). Deletion of a substantial (e.g. up to 9 residues) portion of the peptide structure will inevitably alter both the structural and functional properties of a large number of deletion peptide analogues. The amino acid sequence of the peptide is of great importance in determining the secondary and tertiary structures of the peptide. This is because the peptides structure is determined by the interplay of the hydrophobic/hydrophilic, steric and electrostatic forces among the linked amino acid residues. Deleting a single residue alters these forces in an unpredictable manner; and

consequently, would be expected o alter bioactivity unpredictably. Additionally, applicant. provides only one peptide core structure which is indicated as being critical for pharmaceutical activity (e.g. see specification pages 25-27).

(4) *The level of one of ordinary skill in the art:*

The level of skill would be high, most likely at the Ph.D. level.

(6-7) *The amount of direction provided by the inventor and the existence of working examples.*

The specification discloses pharmaceutical compositions comprising:

(i) a 22-29 residue peptide of formula (I) (elected invention);

(ii) a 15-26 reisidue peptide ... consecutive residues selected from residues selected from residues X1 to X23 of formula (I);

(iii) a 22-29 residue altered peptide ... substituted with another residue ...

and specific peptide compounds of @ 22 amino acids which read on the formula (i) generic.

The specification formula (I) generic and specific species therein are not commensurate to the presently claimed invention broadly encompasses Apo-A-1 agonist compounds which possess attributes (e.g. favorable LCAT activation/helicity/ % hydrophobicity; charged residues/mean hydrophobic moment/mean hydrophobicity/pho angle) but no chemical structure is recited.

Additionally, the specification does not disclose a core structure required for the deletion analogues to maintain their biological activity.

Further, the specification exemplifies a small number of "deletion analogues" which are clearly not commensurate in scope to the presently claimed deletion analogues.

The guidance present in the specification does, in fact, prove the unpredictability of the claimed subject matter. For example, the specification on page 52 (1st full paragraph) describes that, in order to retain activity, a full alpha-helix turn consisting of 3-4 residues must be deleted. This, clearly will not be achieved by deleting a larger number of residues (e.g. 6 residues) which is within the claimed scope of deletion analogs. Additionally, the specification further teaches the critical nature of the "basic cluster at the C-terminus" (e.g. for helix stability) and the importance of the "hydrophobic cluster" at the N-terminus (e.g. effecting lipid binding and LCAT activation) which would provide further evidence of the expected inactivity of a large number of deletion analogs within the scope of the presently claimed invention which lack some or all of the residues within these two critical regions.

Still further, the term "Apo-A-1 agonist" is an unduly broad term which may refer to analogous structure (e.g. amino acid sequence) and/or function (e.g. therapeutic properties) and/or conformation (e.g. the 3D parameters for binding an enzyme, antibody and/or receptor); the parameters of which is neither described, nor representative examples provided, as to enable the skilled artisan to practice the presently claimed invention without undue experimentation. For example, the requisite computer algorithms and crystallization methods and/or techniques are not adequately described in the specification as to permit the skilled artisan to "model" the claimed

peptide so as to determine any requisite secondary and/or tertiary conformation necessary to arrive at a peptide analogue. Nor does the specification provide any description as to degree of homology and/or means of measuring homology (e.g. parameters such as gaps for a particular homology program) which are necessary to practice the presently claimed invention. Nor does the specification discuss what properties

In this regard, it is noted that claims which lack critical or essential subject matter which are necessary to the practice of the invention, but are not included in the claim(s), *including essential compound structure*, will necessarily render the claimed invention nonenabled. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976)(method steps); and *Ex Parte Bhide* (Bd Pat. App. & Int.) 42 USPQ2d 1441 (compound structure).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In view of the large number of Apo-A1 agonist compound and peptide deletion analogues of unrelated peptide structure, the insufficient guidance and working examples regarding Apo-A1 agonist compounds and/or peptide deletion analogues, the unpredictability in the art, the expected criticality of core structure for bioactivity, one skilled in the art could not make and/or use the invention within the claimed breadth without an undue amount of experimentation.

4. Claim 72 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "cluster" in claim 72 is a relative term which renders the claim indefinite. The term "cluster of basic residues" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope (e.g. the number of basic residues) of the invention needed to infringe the presently claimed invention .

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical

Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 63 and 66-86 and 88-93 are rejected under 35 U.S.C. 102(a,b,e) as being anticipated by Segrest et al. US Pat. No. 4,643,988.

The presently claimed invention (e.g. claim 63) is drawn to a pharmaceutical composition comprising "an ApoA-1 agonist" and a pharmaceutically acceptable carrier, excipient or diluent. It is noted that the phrase "an ApoA-1 agonist" is not specifically defined in the specification but are cited a possessing the ability to "mimic Apo-A-I function and activity" with certain attributes being claimed in a dependent manner:

a. "at least about 38% LCAT-activation activity" (claim 66);

b. 15-29-residue peptide or peptide analog that forms an amphipathic alpha-helix in the presence of lipids (claim 67);

- 40-80% helicity in the presence of lipids (claims 68-69);
- comprise 40-70% hydrophobic residues (claims 70-71);
- last C-terminal turn of alpha helix is a "cluster of basic residues" (claim 72);
- at least one acidic residue/turn (claim 73);
- 3-5 charged residues (claims 74-75);
- mean hydrophobic moment is 0.45 to 0.65 (claims 78-79);
- mean hydrophobicity is -.050 to -.07 (claim 80);
- mean hydrophobicity is -.03 to -.055 (claim 81);

- mean hydrophobicity of the hydrophobic face is .9-1.2 (claims 82-83)
- pho angle is 160 degrees to 220 degrees (claim 84-85)

c. in the form of an Apo-A-I agonist/lipid complex (claim 86);

- in solution (claim 89) or lyophilized powder (claim 88);
- is a small unilamellar vesicle (claim 90);
- lipid/peptide molar ratio of 30 (claim 93);
- discoidal peptide complex (claim 91)

which comprises @ 10-@ 14 Apo-A-I agonists peripherally arranged in an antiparallel fashion about at least one lipid (claim 92).

Segrest et al. Teach peptides capable of forming an amphipathic helix (when exposed to lipids) which include both a GENUS of 18 amino acid length peptides (e.g. see formula (i) : col. 3, lines 5-15) as well as individual peptides (e.g. 18naA: see col. 4, lines 21-27; 18A, 17 des A; and 37 pA : see col. 8,lines 17-32) which:

- comprise 15-29-residue peptide or peptide analog that forms an amphipathic alpha-helix in the presence of lipids (anticipating claim 67);
- comprise @ 40-70% hydrophobic residues at least one acidic residue/turn with a "cluster of basic residues at the last C-terminal turn"; 3-5 charged residues and thus must have a net charge of @ –1 to +1 (anticipating claims 71-77);

- forms Apo-AI peptide agonist "discoidal" lipid complexes in solution which is subsequently lyophilized to form a powder or is made into small unilamellar vesicles which stimulate LCAT activity (anticipating claims 86 and 88-91).

See Segrest e.g. figures (e.g. 3-8); col. 3-5; examples (especially example 3); and patent claims.

Regarding the following present claim limitations:

a. the degree of LCAT-activation activity (e.g. at least @ 38%: claim 66);

b. the degree of helicity of peptide/lipid complex (e.g. 40-80%: claims 68-69);

c. mean hydrophobic moment/hydrophobicity (e.g. claims 78-83); and

d. pho angle (e.g. 60 degrees to 220 degrees : claim 84-85)

e. proportion of lipid/peptide (e.g. claims 92-93)

it is noted that since Segrest et al. reference peptides are clearly within the presently claimed scope of chemical structure and/or clearly represent ApoA-1 agonist compounds sharing amino acid composition and /or lipid complexing to form helices andelicit LCAT activation; and contain hydrophobic amino acids and thus should be expected to possess mean hydrophobic moments/hydrophobicity and possess pho anges within the scope of the presently claimed invention as discussed above. Alternatively, the above cited items a-e not explicity taught by the reference would nevertheless be deemed to be inherently present absent evidence to the contrary. In this regard it is noted that the PTO lacks facilities for comparing prior art compounds to compounds within the broad scope of the presently claimed invention; thus shifting the burden to applicant to provide otherwise.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 63 and 66-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Segrest et al. US Pat. No. 4,643,988 and Isliker et al. US Pat. No. US Pat. No. 5,089,602 (2/92).

The presently claimed invention (e.g. claim 63) is drawn to a pharmaceutical composition comprising "an ApoA-1 agonist" and a pharmaceutically acceptable carrier, excipient or diluent. It is noted that the phrase "an ApoA-1 agonist" is not specifically defined in the specification but are cited a possessing the ability to "mimic Apo-A-I function and activity" with certain attributes being claimed in a dependent manner:

a. "at least about 38% LCAT-activation activity" (claim 66);

b. 15-29-residue peptide or peptide analog that forms an amphipathic alpha-helix in the presence of lipids (claim 67);

- 40-80% helicity in the presence of lipids (claims 68-69);
- comprise 40-70% hydrophobic residues (claims 70-71);
- last C-terminal turn of alpha helix is a "cluster of basic residues" (claim 72);
- at least one acidic residue/turn (claim 73);
- 3-5 charged residues (claims 74-75);
- mean hydrophobic moment is 0.45 to 0.65 (claims 78-79);
- mean hydrophobicity is -.050 to -.07 (claim 80);
- mean hydrophobicity is -.03 to -.055 (claim 81);
- mean hydrophobicity of the hydrophobic face is .9-1.2 (claims 82-83)
- pho angle is 160 degrees to 220 degrees (claim 84-85)

c. in the form of an Apo-A-I agonist/lipid complex (claim 86);

- in solution (claim 89) or lyophilized powder (claim 88);
- is a small unilamellar vesicle (claim 90);
- lipid/peptide molar ratio of 30 (claim 93);
- discoidal peptide complex (claim 91)

which comprises @ 10-@ 14 Apo-A-I agonists peripherally arranged in an antiparallel fashion about at least one lipid (claim 92).

Segrest et al. Teach peptides capable of forming an amphipathic helix (when exposed to lipids) which include both a GENUS of 18 amino acid length peptides (e.g. see formula (i) : col. 3, lines 5-15) as well as individual peptides

(e.g. 18naA: see col. 4, lines 21-27; 18A, 17 des A; and 37 pA : see col. 8,lines 17-32) which:

- comprise 15-29-residue peptide or peptide analog that forms an amphipathic alpha-helix in the presence of lipids (anticipating claim 67);
- comprise @ 40-70% hydrophobic residues at least one acidic residue/turn with a "cluster of basic residues at the last C-terminal turn"; 3-5 charged residues and thus must have a net charge of @ –1 to +1 (anticipating claims 71-77);
- forms Apo-AI peptide agonist "discoidal" lipid complexes in solution which is subsequently lyophilized to form a powder or is made into small unilamellar vesicles which stimulate LCAT activity (anticipating claims 86 and 88-91).

See Segrest e.g. figures (e.g. 3-8); col. 3-5; examples (especially example 3); and patent claims.

Regarding the following present claim limitations:

a. the degree of LCAT-activation activity (e.g. at least @ 38%: claim 66);

b. the degree of helicity of peptide/lipid complex (e.g. 40-80%: claims 68-69);

c. mean hydrophobic moment/hydrophobicity (e.g. claims 78-83); and

d. pho angle (e.g. 60 degrees to 220 degrees : claim 84-85)

e. proportion of lipid/peptide (e.g. claims 92-93)

it is noted that since Segrest et al. reference peptides are clearly within the presently claimed scope of chemical structure and/or clearly represent ApoA-1 agonist compounds sharing amino acid composition and /or lipid complexing to form helices

andelicit LCAT activation; and contain hydrophobic amino acids and thus should be expected to possess mean hydrophobic moments/hydrophobicity and possess pho anges within the scope of the presently claimed invention as discussed above. Alternatively, the above-cited items a-e not explicity taught by the reference would nevertheless be deemed to be inherently present absent evidence to the contrary. In this regard it is noted that the PTO lacks facilities for comparing prior art compounds to compounds within the broad scope of the presently claimed invention; thus shifting the burden to applicant to provide otherwise.

The Segrest reference differs from the presently claimed invention by failing to teach forming an Apo-A-I agonist-lipid complex using sphingomyelin as the lipid (e.g. present claim 87).

In this regard, it is noted that the Segrest reference teaches the use of their peptides (e.g. formula I) :

a. to spontaneously interact at room temperature with phospholipids to form small, soluble discoidal HDL-like complexes which then may be used as "substitute high-density lipoprotein in the plasma, providing the same protective effect against atherosclerosis in the bloodstream as native HDL would"; and

b. the phospholipids used for the formation of the complex may vary, but includes egg phosphatidyl choline (PC), dimyristoyl PC (DMPC), and dipalmitoyl phosphatidylcholine (DPPMC).

Isliker teaches that HDL are complexes composed of lipids (e.g. PC , sphingomyelin, as and cholesterol or esters thereof) and apoproteins (e.g. apoA-1/II/E). E.g. see col. 1, especially lines 55-68.

One of ordinary skill in the art would be motivated to utilize sphingomyelin as the lipid to form complexes in accordance with the Segrest reference since:

a. Segrest teaches that different phospholipids can be used to form its peptide/lipid complexes; and

b. Isliker teaches that in addition to PC, sphingomyelin and cholesterol are lipids to which is present in HDL and there would be motivation to select sphingomyelin to make the Segrest HDL mimics.

Additionally, the selection of sphingomyelin from a small number of alternative lipids comprising HDL would be immediately envisaged or alternatively prima facie obvious to one of ordinary skill in the art.

Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to utilize sphingomyeliin as disclosed in the Islliker refence for use as the lipid in forming Apo-AI agonist-lipid complexes in accordance with the Segrest reference for the purpose of making HDL mimics for intended therapeutic use.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 63 and 66-93 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

i. claims 1, 19-21, 28, 36, 41, 43-46, 53 and 56-57 of 10/937,767 (PG PUB: 2005/0080013 A1;

ii. claims 53-83 of 10/801,897 (PG PUB: 2004/0198662A1);

iii. claims 1-52 of 09/865,989 (PG PUB: 2004/0029807 A9);

iv. claims 1-55 of 10/099,574 (PG PUB: 2003/0060604A1); and

iv. claims 1-52 of 09/865,989 (PG PUB: 2003/0008827A1.

The claims in the above-cited applications teach pharmaceutical compositions comprising Apo-A1 agonist peptide compounds comprising 15-29 residues comprising charged residues (e.g. 3-5) and hydrophobic residues (e.g. 40-70%) within the scope of the presently claimed invention which further form an amphipathic helix in the presence of lipids (e.g. an "ApoA-I agonist "discoidal" lipid complex) with @ 38% which form LCAT activation.

Regarding limitations if not explicitly taught by the application claims e.g.:

a. the degree of helicity of peptide/lipid complex (e.g. 40-80%: claims 68-69);

b. mean hydrophobic moment/hydrophobicity (e.g. claims 78-83); and

c. pho angle (e.g. 60 degrees to 220 degrees : claim 84-85)

d. proportion of lipid/peptide (e.g. claims 92-93)

it is noted that the application claim peptides are clearly within the presently claimed scope of chemical structure and/or clearly represent ApoA-1 agonist compounds sharing amino acid composition and /or lipid complexing to form helices and LCAT activation; and contain hydrophobic amino acids and thus should be expected to possess mean hydrophobic moments/hydrophobicity and possess pho anges within the scope of the presently claimed invention as discussed above. Alternatively, the above cited items a-d not explicity taught by the reference would nevertheless be deemed to be inherently present absent evidence to the contrary. In this regard it is noted that the PTO lacks facilities for comparing prior art compounds to compounds within the broad scope of the presently claimed invention; thus shifting the burden to applicant to provide otherwise.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 63, 66-101, 103-104 and 110 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

i. claims 1-68 of copending Application No. 10/283,599 (PG PUB. 2003/0208059A1);

ii. claims 1-56 of copending Application No. 10/099,836 (PG PUB 2003/0203842A1)

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the above-cited applications teach pharmaceutical compositions comprising Apo-A1 agonist peptide compounds (INCLUDING ELECTED SPECIES OF SEQ. ID : 4) comprising 15-29 residues comprising charged residues (e.g. 3-5) and hydrophobic residues (e.g. 40-70%) within the scope of the presently claimed invention which further form an amphipathic helix in the presence of lipids (e.g. an "ApoA-I agonist "discoidal" lipid complex) with @ 38% which form LCAT activation.

Regarding limitations if not explicitly taught by the application claims e.g.:

a. the degree of helicity of peptide/lipid complex (e.g. 40-80%: claims 68-69);

b. mean hydrophobic moment/hydrophobicity (e.g. claims 78-83); and

c. pho angle (e.g. 60 degrees to 220 degrees : claim 84-85)

d. proportion of lipid/peptide (e.g. claims 92-93)

it is noted that the application claim peptides are clearly within the presently claimed scope of chemical structure and/or clearly represent ApoA-1 agonist compounds sharing amino acid composition and /or lipid complexing to form helices and LCAT activation; and contain hydrophobic amino acids and thus should be expected to possess mean hydrophobic moments/hydrophobicity and possess pho anges within the scope of the presently claimed invention as discussed above. Alternatively, the above cited items a-d not explicity taught by the reference would nevertheless be deemed to be inherently present absent evidence to the contrary. In this regard it is noted that the PTO lacks facilities for comparing prior art compounds to compounds within the broad

scope of the presently claimed invention; thus shifting the burden to applicant to provide otherwise.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 63 and 66-93 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

i. claims 1-34 of U.S. Patent No. 6,573,239;

ii.claims 1-48 of U.S. Patent No. 6,265,377;

iii. claims 1-49 of U.S. Patent No. 6,046,166; and

iv. claims 1-54 of U.S. Patent No. 6,037,323.

. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the above-cited patents teach pharmaceutical compositions comprising Apo-A1 agonist peptide compounds comprising 15-29 residues comprising charged residues (e.g. 3-5) and hydrophobic residues (e.g. 40-70%) within the scope of the presently claimed invention which further form an amphipathic helix in the presence of lipids (e.g. an "ApoA-I agonist "discoidal" lipid complex) with @ 38% which form LCAT activation.

Regarding limitations if not explicitly taught by the application claims e.g.:

a. the degree of helicity of peptide/lipid complex (e.g. 40-80%: claims 68-69);

b. mean hydrophobic moment/hydrophobicity (e.g. claims 78-83); and

c. pho angle (e.g. 60 degrees to 220 degrees : claim 84-85)

d. proportion of lipid/peptide (e.g. claims 92-93)

it is noted that the application claim peptides are clearly within the presently claimed scope of chemical structure and/or clearly represent ApoA-1 agonist compounds sharing amino acid composition and /or lipid complexing to form helices and LCAT activation; and contain hydrophobic amino acids and thus should be expected to possess mean hydrophobic moments/hydrophobicity and possess pho anges within the scope of the presently claimed invention as discussed above. Alternatively, the above cited items a-d not explicity taught by the reference would nevertheless be deemed to be inherently present absent evidence to the contrary. In this regard it is noted that the PTO lacks facilities for comparing prior art compounds to compounds within the broad scope of the presently claimed invention; thus shifting the burden to applicant to provide otherwise.

14. Claims 63,66-101, 103-104 and 110 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over:

i. claims 1-48 of U.S. Pat. No.6,753,313;

ii. claims 1-58 of U.S. Pat. No. 6,716,816;

iii. claims 1-36 of U.S. Pat. No. 6,630,450;

iv. claims 1-38 of U. S. Pat. No. 6,602,854;

v. claims 1-9 of U.S. Pat. No. 6,518,412;

vi. claims 1-21 of U.S. Pat. No. 6,376,464;

vii. claims 1-21 of U.S. Pat. No. 6,329,341; and

viii. claims 1-58 of U.S. Pat. No. 6,004,925.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the above-cited patents teach pharmaceutical compositions comprising Apo-A1 agonist peptide compounds (INCLUDING ELECTED SPECIES OF SEQ. ID : 4) comprising 15-29 residues comprising charged residues (e.g. 3-5) and hydrophobic residues (e.g. 40-70%) within the scope of the presently claimed invention which further form an amphipathic helix in the presence of lipids (e.g. an "ApoA-I agonist "discoidal" lipid complex) with @ 38% which form LCAT activation.

Regarding limitations if not explicitly taught by the application claims e.g.:

a. the degree of helicity of peptide/lipid complex (e.g. 40-80%: claims 68-69);

b. mean hydrophobic moment/hydrophobicity (e.g. claims 78-83); and

c. pho angle (e.g. 60 degrees to 220 degrees : claim 84-85)

d. proportion of lipid/peptide (e.g. claims 92-93)

it is noted that the application claim peptides are clearly within the presently claimed scope of chemical structure and/or clearly represent ApoA-1 agonist compounds sharing amino acid composition and /or lipid complexing to form helices and LCAT activation; and contain hydrophobic amino acids and thus should be expected to possess mean hydrophobic moments/hydrophobicity and possess pho anges within the scope of the presently claimed invention as discussed above. Alternatively, the above cited items a-d not explicity taught by the reference would nevertheless be deemed to be inherently present absent evidence to the contrary. In this regard it is noted that the PTO lacks facilities for comparing prior art compounds to compounds within the broad

scope of the presently claimed invention; thus shifting the burden to applicant to provide otherwise.

Future Correspondences:

.Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bennett Celsa whose telephone number is 571-272-0807. The examiner can normally be reached on 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bennett Celsa
Primary Examiner
Art Unit 1639

BC
April 19, 2005